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MODELING MALARIA SENSITIVE AND RESISTANT STRAINS WITH SUPERINFECTION

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Abstract. In this paper, a deterministic model to examine the dynamics of malaria with sensitive and resistant strains in the presence of superinfection is formulated and presented. The basic reproduction is computed using next-generation method and sensitivity index for each parameter with respect to reproduction number R_0 is derived. The rate at which human beings are infected by malaria resistant strain and mosquitoes' mortality rate are the most sensitive parameters to malaria transmission dynamics. Though analysis shows that the rates at which humans are infected by resistant strain and mosquitoes' natural mortality rate are more sensitive to the disease transmission dynamics, still mosquitoes' biting rate plays an important role in the transmission dynamics of malaria. To control malaria infection, interventions which increase mosquitoes' natural mortality, and decrease their biting rate are recommended.

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1. Introduction

Malaria is an infectious disease which is caused by protozoan parasites belonging to the genus *Plasmodium* and spread by female *Anopheles* species mosquitoes [7]. *Plasmodium* parasites which cause malaria in human beings are; *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium vivax* [19]. Among the four *Plasmodium* parasites, *Plasmodium falciparum* causes the most virulent form of malaria in human [11]. The mosquito-borne parasites spread from one human to another by the bite of *Anopheles* female mosquito which consumes human blood [16, 17, 20].

Mosquitoes also suffer from malaria infection, a meal from infected human being by susceptible *Anopheles* female mosquito results into a transmission of malaria parasites to a susceptible mosquito and in the same way, a meal by an infected mosquito from susceptible human results into malaria infection to a human being. The *Plasmodium* consist of two different phases; sexual and asexual phases, the asexual phase comprise of three forms: sporozoites, merozoites and trophozoites [18]. The infection cycle begins when sporozoites are injected by a mosquito and are carried into the body. Sporozoites then attack the liver hepatocytes where they undergo asexual multiplication resulting into merozoites [10]. The merozoites flood out into the blood and invade red blood cells where they initiate a second phase of asexual multiplication resulting into reproduction of about 8 - 16 merozoites which infect new red blood cells and destroy them completely.

Although malaria is a curable disease, emergence of drug resistant strain is making malaria infection more difficult to treat and control [13]. This form of malaria does not respond to malaria drugs which are the first line treatment. The causes of malaria with resistant strain include infection with *Plasmodium falciparum* which is the most virulent form of malaria parasite [8], movement of community from one place to another and mutation of malaria parasites [19, 11]. Though treatment of resistant strain recommends combination therapy, it is not easily accessible since it is given only to a person who has been diagnosed with malaria resistant strain.

A mosquito with drug resistant strain transmits resistant malaria to human and human being with resistant malaria does the same to the mosquito. As proposed by Klein et al. [12], a

mosquito can have both strains; drug sensitive and resistant strains which is termed as superinfection. A blood meal from a human being by a mosquito with both strains results into malaria with both strains and a blood meal from a human being which is infected with both strains can infect a susceptible mosquito with sensitive and resistant strains. The aim of this work is to study transmission dynamics of malaria with super infection.

Studies have addressed dynamics of malaria with sensitive and resistant strains [2, 5, 9, 19, 22,12] and less consider the role of mosquito in transmitting both sensitive and resistant strains which is termed superinfection. A study by Tumwiine et al. [19] concentrated on resistant and sensitive strains by assuming that among infected humans, a proportion $1 - \theta$ acquires resistant strain and θ acquire sensitive strain. However the study does not consider multiple strains which we call superinfection as suggested by Klein et al. [12].

A cohort study by by Aneke [2] acknowledges that there are mosquitoes which have malaria resistant parasites and they transmit drug resistant malaria. However, the study did not put emphasize on malaria drug resistance strains which affects the overall dynamics of malaria. Apart from that, Sensitive and Resistant malaria strains are not well explained. The study assumed that the infected mosquito with malaria resistant strain has both strains and can transmit both resistant and sensitive strains at the same time though superinfection is not considered.

This study is conducted to study transmission dynamics of malaria where the role of mosquitoes in transmitting both sensitive and resistant strains with superinfection is considered.

2. Materials and Methods

2.1 Model Development

The model development is based on Esteva et al. [9] model, which divides human population into susceptible S_h , treated humans with wild type $I_W(t)$, humans infected with resistant strain $I_R(t)$, and the mosquito population is divided into Susceptible vectors $S_V(t)$, and vectors which are infected with resistant strain $V_R(t)$. The proposed model divides human population into five compartments which are susceptible S_h , infectious with sensitive strain I_{hs} , infectious with resistant strain I_{hr} , infectious with both strains I_{hsr} and recovery R_h . Mosquitoes' population is

divided into four compartments which are susceptible S_m , infectious with sensitive strain I_{ms} , infectious with resistant strain I_{mr} and infectious with both strains I_{mr} .

Human susceptible class S_h is recruited by birth and immigration at a constant rate Λ_m , following a blood meal from mosquitoes which are infected with sensitive, resistant and both strains, the class suffers malaria infection with sensitive, resistant and both strains at rates β_s , β_r and β_b respectively. Infectious class with sensitive strain I_s flourish due to infection of susceptible class at a rate β_s and competition of malaria parasites within individuals who are infected with both strains where sensitive strain becomes fit compared to a resistant strain at a rate c_s . The class diminish due to recovery and malaria induced death due to resistant strain at rates k_s and α_s respectively.

The class which is infected with both strains I_{hsr} increase due to infection of susceptible humans at a rate β_b . It deteriorates due to competition where sensitive and resistant strains become fit at rates c_s and c_r . It further decreases due to recovery and disease mortality at rates k_b and α_b respectively. Infectious class with resistant strain I_r is replenished by infection of susceptible human and competition in individuals who are infected with both strains where sensitive strain becomes fit compared to a resistant strain at rates β_r and c_r respectively. All human compartments suffer natural mortality at a rate μ_h .

The susceptible mosquito S_m is recruited at a rate Λ_m . It suffers malaria infection following a blood meal from humans who are infected with sensitive, resistant and both strains at rates β_{ms} , β_{mr} and β_{mb} respectively. The mosquitoes' infectious class with sensitive strains I_{ms} is refilled by infection of susceptible mosquitoes and competition within mosquitoes which are infected with both strains where sensitive strain becomes fit at rates β_{ms} and c_{ms} respectively. It suffers disease induced mortality at a rate α_{ms} .

The mosquito class which is infected by both strains grow in number when susceptible mosquitoes feed on human being who are infected with both strain at a rate β_{mb} . However it reduces due to disease induced mortality and competition of resistant and sensitive strain at rates α_{mb} , c_{ms} and c_{mr} respectively. Infectious mosquitoes with resistant strain flourish following infection of susceptible mosquitoes with resistant strain at a rate β_{mr} and competition within mosquitoes which are infected with both strains where resistant strain becomes fit at a rate c_{mr} .

The class suffers disease induced mortality at a rate α_{mr} . All mosquitoes compartment suffers natural mortality at a rate μ_m .

2.2 Model Assumptions

The model assumes that mosquitoes which have both strains are responsible for their transmission and this is called superinfection. There is always competition between sensitive and resistant strains, if sensitive strain becomes fit then human or mosquito which is infected with both strains becomes infected with sensitive strain and contrary happens when resistant strain becomes fit. Vertical transmission is not considered. Malaria exposed stage is neglected due to its short incubation period. All individuals are born susceptible to malaria infection.

2.3 Model Equations

Human equations

$$\begin{aligned}
 (1a) \quad \frac{dS_h}{dt} &= \Lambda_h + \rho R_h - \frac{\beta_s I_{ms} S_h}{N_h} - \frac{\beta_r I_{mr} S_h}{N_h} - \frac{\beta_b I_{msr} S_h}{N_h} - \mu_h S_h, \\
 (1b) \quad \frac{dI_{hs}}{dt} &= \frac{\beta_s I_{ms} S_h}{N_h} + c_s I_{hsr} - (k_s + \alpha_s + \mu_h) I_{hs}, \\
 (1c) \quad \frac{dI_{hr}}{dt} &= \frac{\beta_r I_{mr} S_h}{N_h} + c_r I_{hsr} - (k_r + \alpha_r + \mu_h) I_{hr}, \\
 (1d) \quad \frac{dI_{hsr}}{dt} &= \frac{\beta_b I_{msr} S_h}{N_h} - (k_b + \alpha_b + c_s + c_r + \mu_h) I_{hsr}, \\
 (1e) \quad \frac{dR_h}{dt} &= k_s I_{hs} + k_r I_{hr} + k_b I_{hsr} - (\rho + \mu_h) R_h,
 \end{aligned}$$

Mosquitoes Equations

$$\begin{aligned}
 (2a) \quad \frac{dS_m}{dt} &= \Lambda_m - \frac{\beta_{ms} I_{hs} S_m}{N_h} - \frac{\beta_{mr} I_{hr} S_m}{N_h} - \frac{\beta_{mb} I_{hsr} S_m}{N_h} - \mu_m S_m, \\
 (2b) \quad \frac{dI_{ms}}{dt} &= \frac{\beta_{ms} I_{hs} S_m}{N_h} + c_{ms} I_{msr} - (\alpha_{ms} + \mu_m) I_{ms}, \\
 (2c) \quad \frac{dI_{mr}}{dt} &= \frac{\beta_{mr} I_{hr} S_m}{N_h} + c_{mr} I_{msr} - (\alpha_{mr} + \mu_m) I_{mr}, \\
 (2d) \quad \frac{dI_{msr}}{dt} &= \frac{\beta_{mb} I_{hsr} S_m}{N_h} - (c_{ms} + c_{mr} + \alpha_{mb} + \mu_m) I_{msr},
 \end{aligned}$$

subject to initial conditions:

$$S_h > 0, I_{hs} \geq 0, I_{hr} \geq 0, I_{hsr} \geq 0, R_h \geq 0, S_m \geq 0, I_{ms} \geq 0, I_{mr} \geq 0, I_{msr} \geq 0.$$

The total human population is given by;

$$(3) \quad N_h = S_h + I_{hs} + I_{hr} + I_{hsr} + R_h.$$

The total mosquito population is given by;

$$(4) \quad N_m = S_m + I_{ms} + I_{mr} + I_{msr}.$$

3. Model Analysis

Before we analyze the model equilibrium states, we assess whether the model is mathematically and epidemiologically meaningful or not. To do so, we study the model solutions to determine if they are bounded and positive.

3.1 Invariant region

We assume that all the variables and parameters of the model are positive for all $t \geq 0$. To study the invariant region, we consider the total population for human and mosquitoes as in equations (3) and (4). The change of human population with respect to time is

$$(5) \quad \frac{dS_h}{dt} \geq \Lambda_h - \mu_h N_h.$$

Integrating (5) and applying Birkhoff and Rota [3] theorem in equation (5) and as $t \rightarrow \infty$, we get:

$$0 \leq N_h(t) \leq \frac{\Lambda_h}{\mu_h},$$

This indicates that, when there is no disease the human population cannot be zero and it cannot exceed $\frac{\Lambda_h}{\mu_h}$. Similarly, the change of mosquitoes' population given in equation (4) is

$$(6) \quad \frac{dS_m}{dt} \geq \Lambda_m - \mu_m N_m.$$

Integrating equation (6) and applying the initial conditions, we obtain

$$(7) \quad N_m(t) \leq \frac{\Lambda_m}{\mu_m} + \left(N_m(0) - \frac{\Lambda_m}{\mu_m} \right) e^{-\mu t},$$

Applying Birkhoff and Rota [3] theorem on differential inequality as $t \rightarrow \infty$ in equation (7), we obtain

$$0 \leq N_m(t) \leq \frac{\Lambda_m}{\mu_m},$$

This indicates that, in the absence of disease population cannot exceed $\frac{\Lambda_m}{\mu_m}$. Therefore, the feasible solution set of the population of the system enters the region

$$(8) \quad \Omega = \left\{ (S_h, I_{hs}, I_{hr}, I_{hsr}, R_h, S_m, I_{ms}, I_{mr}, I_{msr}) \in R_+^9 : 0 \leq N_h(t) \leq \frac{\Lambda_h}{\mu_h}, 0 \leq N_m(t) \leq \frac{\Lambda_m}{\mu_m} \right\}$$

3.2 Positivity of solutions

For model (1a) - (2d) to be epidemiologically meaningful, we need to prove that all state variables are non-negative $t \geq 0$. Let the initial value be

$\{S_h(0) > 0, S_m(0) > 0, (I_{hs}(0), I_{hr}(0), I_{hsr}(0), R_h(0), I_{ms}(0), I_{mr}(0), I_{msr}(0)) \geq 0\} \in \Omega$ the solution set $\{S_h, I_{hs}, I_{hr}, I_{hsr}, R_h, S_m, I_{ms}, I_{mr}, I_{msr}\}$ of the model system

(1a) - (2d) is non-negative for all $t > 0$. To prove that we have;

$$\begin{aligned} \frac{dS_h}{dt} &= \Lambda_h + \rho R_h - \frac{\beta_s I_{ms} S_h}{N_h} - \frac{\beta_r I_{mr} S_h}{N_h} - \frac{\beta_b I_{mb} S_h}{N_h} - \mu_h S_h, \\ \int \frac{dS_h}{S_h} &\geq - \int_0^t \left(\frac{\beta_s I_{ms}}{N_h} + \frac{\beta_r I_{mr}}{N_h} + \frac{\beta_b I_{mb}}{N_h} + \mu_h \right) dt, \\ S_h(t) &\geq S_h(0) e^{\int_0^t - \left(\frac{\beta_s I_{ms}(s)}{N_h(s)} + \frac{\beta_r I_{mr}(s)}{N_h(s)} + \frac{\beta_b I_{msr}(s)}{N_h(s)} + \mu_h \right) ds} \geq 0, \end{aligned}$$

Applying similar approach for equation (1b) - (2d) we have

$$\begin{aligned} I_{hs} &\geq I_{hs}(0) e^{-(k_s + \alpha_s + \mu_h)t} \geq 0, \\ I_{hr} &\geq I_{hr}(0) e^{-(k_r + \alpha_r + \mu_h)t} \geq 0, \\ I_{hsr} &\geq I_{hsr}(0) e^{-(k_b + c_s + c_r + \alpha_b + \mu_h)t} \geq 0, \\ R_h &\geq R_h(0) e^{-(\rho + \mu_h)t} \geq 0, \\ S_m(t) &\geq S_m(0) e^{\int_0^t - \left(\frac{\beta_{ms} I_{hs}(s)}{N_h(s)} + \frac{\beta_{mr} I_{hr}(s)}{N_h(s)} + \frac{\beta_{mb} I_{msr}(s)}{N_h(s)} + \mu_h \right) ds} \geq 0, \\ I_{ms}(t) &\geq I_{ms}(0) e^{-(\mu_m + \alpha_{ms})t} \geq 0, \\ I_{mr}(t) &\geq I_{mr}(0) e^{-(\alpha_{mr} + \mu_m)t} \geq 0, \\ I_{msr}(t) &\geq I_{msr}(0) e^{-(c_{ms} + c_{mr} + \alpha_{mb} + \mu_m)t} \geq 0. \end{aligned}$$

This shows that, the solution set $\{S_h, I_{hs}, I_{hr}, I_{hsr}, R_h, S_m, I_{ms}, I_{mr}, I_{msr}\}$ of the model equation (1a) - (2a) is non-negative $\forall t \geq 0$.

3.3 Disease Free Equilibrium

The disease free equilibrium is a steady state in which there is no infection. We obtain disease-free equilibrium when diseased groups are zero. That is $I_{hs} = I_{hr} = I_{hsr}, R_h = S_m = I_{ms} = I_{mr} = I_{msr} = 0$. Disease free equilibrium is given by:

$$(9) \quad E^0(S_h, I_{hs}, I_{hr}, I_{hsr}, R_h, S_m, I_{ms}, I_{mr}, I_{msr}) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, 0, \frac{\Lambda_m}{\mu_m}, 0, 0, 0 \right)$$

When there is no malaria infection, the whole human population is susceptible.

3.4 The Basic Reproduction Number (R_0)

Equilibrium points are analyzed by considering the threshold quantity called basic reproduction number (R_0). The basic reproduction number (R_0), is a key parameter which determines the behavior of the disease. The disease persists if $R_0 > 1$ and it declines when $R_0 < 1$. It also determines the local stability of the equilibrium states. Disease free equilibrium is asymptotically stable when $R_0 < 1$ and endemic equilibrium is stable when $R_0 > 1$.

The next generation matrix operator which has been established by Van den Driessche and Watmough [21] is used to compute basic reproduction number R_0 . To compute basic reproduction number R_0 , the system (1a) - (2d) is rearranged by starting with infected classes. If new infections and transfer terms are denoted by F_i and V_i respectively then the basic reproduction number R_0 is given by:

$$(10) \quad R_0 = \rho(FV^{-1}).$$

That is the maximum eigenvalue of the matrix FV^{-1} , where

$$(11) \quad F = \frac{\partial (F_i)}{\partial (X_j)} (E^0) \text{ and } V = \frac{\partial (V_i)}{\partial (X_j)} (E^0).$$

The model comprised of the system of equations; $X' = F_i - V_i$ such that $V_i = V_i^- - V_i^+$ where V_i^+ is the rates of transfer of individuals into the compartment and V_i^- is the rate of transfer of individuals out of the compartment. By using the model system (1a) - (2d) and the approach in Van den Driessche and Watmough [21], F_i and V_i are defined as:

$$F_i = \begin{bmatrix} \frac{\beta_s I_{ms} S_h}{N_h} \\ \frac{\beta_r I_{mr} S_h}{N_h} \\ \frac{\beta_b I_{msr} S_h}{N_h} \\ \frac{\beta_{ms} I_{hs} S_m}{N_h} \\ \frac{\beta_{mr} I_{hr} S_m}{N_h} \\ \frac{\beta_{mb} I_{hsr} S_m}{N_h} \end{bmatrix} \text{ and } V_i = \begin{bmatrix} a_s I_{hs} - c_s I_{hsr} \\ a_r I_{hr} - c_r I_{hsr} \\ a_b I_{hsr} \\ a_{ms} I_{ms} - c_{ms} I_{msr} \\ a_{mr} I_{mr} - c_{mr} I_{msr} \\ a_{mb} I_{msr} \end{bmatrix},$$

where;

$$a_s = k_s + \alpha_s + \mu_h, a_r = k_r + \alpha_r + \mu_h, a_b = k_b + \alpha_b + c_s + c_r + \mu_h, a_{ms} = \alpha_{ms} + \mu_m, \\ a_{mr} = \alpha_{mr} + \mu_m, a_{mb} = c_{ms} + c_{mr} + \alpha_{mb} + \mu_m.$$

The matrices F and V work out to be

$$(12) \quad FV^{-1} = \begin{bmatrix} 0 & 0 & 0 & \frac{\beta_s}{a_{ms}} & 0 & \frac{\beta_s c_{ms}}{a_{mb} a_{ms}} \\ 0 & 0 & 0 & 0 & \frac{\beta_r}{a_{mr}} & \frac{\beta_r c_{mr}}{a_{mr} a_{mb}} \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_b}{a_{mb}} \\ \frac{\beta_{ms} \Lambda_m \mu_h}{\Lambda_h \mu_m a_s} & 0 & \frac{\beta_{ms} \Lambda_m \mu_h c_s}{\Lambda_h \mu_m a_s a_b} & 0 & 0 & 0 \\ 0 & \frac{\beta_{mr} \Lambda_m \mu_h}{\Lambda_h \mu_m a_r} & \frac{\beta_{mr} \Lambda_m \mu_h c_r}{\Lambda_h \mu_m a_r a_b} & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_{mb} \Lambda_m \mu_h}{\Lambda_h \mu_m a_b} & 0 & 0 & 0 \end{bmatrix}.$$

The basic reproduction number R_0 is given by

$$(13) \quad R_0 = \max \{R_{01}, R_{02}, R_{03}\}$$

where:

$$R_{01} = \sqrt{\frac{\beta_{ms} \Lambda_m \mu_h \beta_s}{\mu_m \Lambda_h (k_s + \alpha_s + \mu_h) (\alpha_{ms} + \mu_m)}}, R_{02} = \sqrt{\frac{\beta_{mr} \Lambda_m \mu_h \beta_r}{\mu_m \Lambda_h (k_r + \alpha_r + \mu_h) (\alpha_{mr} + \mu_m)}}, \\ R_{03} = \sqrt{\frac{\beta_{mb} \Lambda_m \mu_h \beta_b}{\mu_m \Lambda_h (k_b + \alpha_b + c_s + c_r + \mu_h) (c_{ms} + c_{mr} + \alpha_{mb} + \mu_m)}}.$$

The partial reproduction number R_{01} defines secondary infections for sensitive strain, R_{02} secondary infections for resistant strain and R_{03} secondary infections for both strains. All partial reproduction numbers depend on human and mosquitoes infection rates, the ratio of mosquitoes to human beings initial populations and the average infectious periods in all infected classes. Malaria secondary infections in sensitive, resistant and in both strains will increase when the population of mosquitoes increases, the rate at which mosquitoes in each infected class bite susceptible human beings and the rate at which susceptible mosquitoes bite infected human beings in each infected class. Malaria sensitive strain, malaria resistant strain and malaria with both strains will persist depending on which partial reproduction number is greater than the other. Malaria sensitive strain will persist when $R_{01} > (R_{02}, R_{03})$, and malaria resistant strain will persist when $R_{02} > (R_{01}, R_{03})$, and when $R_{03} > (R_{01}, R_{02})$ malaria with both strains(sensitive and resistant strain) will persist.

3.5 Sensitivity Analysis of basic reproduction number R_0

In this section forward sensitivity analysis of basic reproduction number R_0 with respect to its parameters is performed to determine which parameters influence disease transmission in the population. The forward sensitivity index of parameter p with respect to basic reproduction R_0 is denoted by $\Psi_p^{R_0}$. Using the approach in Selemani et al. [18] and Chuma et al. [6], the normalized forward sensitivity index of a parameter p with respect to basic reproduction number R_0 is defined by:

$$(14) \quad \Psi_p^{R_0} = \frac{\partial (R_0)}{\partial (p)} \times \frac{p}{R_0}.$$

Using parameter values in Table 1 and definition in equation (14), the sensitivity index of each partial reproduction number with respect to its parameters are given in Tables 2, 3 and 4

TABLE 1. Parameter values for Model (1a)-(2d)

Parameter	Value	Source
β_s	0.86/day	[5]

Continued on next page

Table 1 – *Continued from previous page*

Parameter	Value	Source
β_r	0.83/day	[5]
β_b	0.845/day	Assumed
β_{mr}	0.5561/day	[14]
β_{ms}	0.0927/day	[14]
β_{mb}	0.3244/day	Assumed
Λ_h	0.03285/day	[4]
Λ_m	0.071/day	[1],[16]
μ_h	(0.0004-0.017)/day	[20],[15], [1]
μ_m	(0.04-0.05)/day	[19],[1],[15]
α_s	0.002/day	Assumed
k_s	(0.0022-0.0078)/day	[9],[19], [15]
α_r	0.002/day	Assumed
α_b	0.001/day	Assumed
α_{ms}	0.04/day	[15]
α_{mr}	0.04/day	[15]
α_{mb}	0.02/day	Assumed
c_{ms}	0.1236/day	Assumed
c_{mr}	0.7415/day	Assumed
c_r	0.00025/day	Assumed
c_s	0.00005/day	Assumed
k_b	0.0073/day	Assumed
ρ	(0.0125-0.002)/day	[1],[15]
k_r	(0.001-0.0061)/day	[9],[15],[19]

TABLE 2. Sensitivity Indices for R_{01}

Parameter	Sensitivity Index
β_s	+0.5
β_{ms}	+10.7137
α_{ms}	-0.2222
α_s	-0.04132
k_s	-0.0455
Λ_h	-0.5
Λ_m	+0.5
μ_h	+0.0868
μ_m	-0.7778

TABLE 3. Sensitivity Indices for R_{02}

Parameter	Sensitivity Index
β_r	+0.5
β_{mr}	+0.4999
α_{mr}	-0.2222
α_r	-0.0356
k_r	-0.1085
Λ_h	-0.5
Λ_m	+0.5
μ_h	+0.1441
μ_m	-0.7778

TABLE 4. Sensitivity Indices for R_{03}

Parameter	Sensitivity Index
β_b	+0.5
β_{mb}	+0.1919
α_b	-0.0506
k_b	-0.1193
Λ_h	-0.5
Λ_m	+0.5
μ_h	+0.1732
μ_m	-0.5272
c_s	-0.00082
c_r	-0.00408
c_{ms}	-0.0673
c_{mr}	-0.4038

The positive indices indicate that the basic reproduction number increases as the value of the parameter increases, and the negative index value indicates the inverse relationship between the partial reproduction number and the given parameter.

In Table 2, parameters β_s , β_{ms} , Λ_m , and μ_h have positive indices. This show that, partial reproduction number R_{01} is direct proportional to the rate of human infected by sensitive β_s , rate of mosquito infected by sensitive β_{ms} , recruitment rate of mosquito population Λ_m and natural death rate of human μ_h . The most sensitive parameter is the rate at which mosquitoes are infected with malaria sensitive strain β_{ms} . Natural death rate of human μ_h is the least sensitive index value.

The negative indexed parameters are α_{ms} , α_s , k_s , Λ_h and μ_m . According to these results, natural death rate of mosquito μ_m is the most negative sensitive parameter in the model. This indicates that secondary infections for malaria with sensitive strain decrease as many mosquitoes die.

In Table 3, parameters β_r , β_{mr} , Λ_m and μ_h have positive indices. These parameters have positive influence on partial reproduction number R_{02} . The rate at which human are infected with resistant strain β_r is the most sensitive parameter of the model, the least sensitive index values is natural death rate of human μ_h .

The negative indexed parameters are μ_m , Λ_h , α_{mr} , α_r and k_r . These results show that, natural death rate of mosquito μ_m , is the most negative sensitive parameter of the model. This indicates that secondary infection for malaria with resistant strain will decrease as infected mosquito decrease.

In Table 4, positive indexed parameters are β_b , β_{mb} , Λ_m , and μ_h . These parameters have positive influence on partial reproduction number R_{03} . The most positive sensitive parameter of the model is the rate of human infected by both strains β_b .

The negative index values Parameters are c_m , c_r , c_s , c_{ms} , k_b , c_{mr} , μ_m , Λ_h . The most negative index value is μ_m . According to these results, competition due to sensitive c_s is the least negative sensitive parameter in the model.

4. Numerical Simulation

To determine the effect of sensitive parameters on the dynamics of malaria with sensitive and resistant strains with superinfection, we simulate the model using parameters in Table 1.

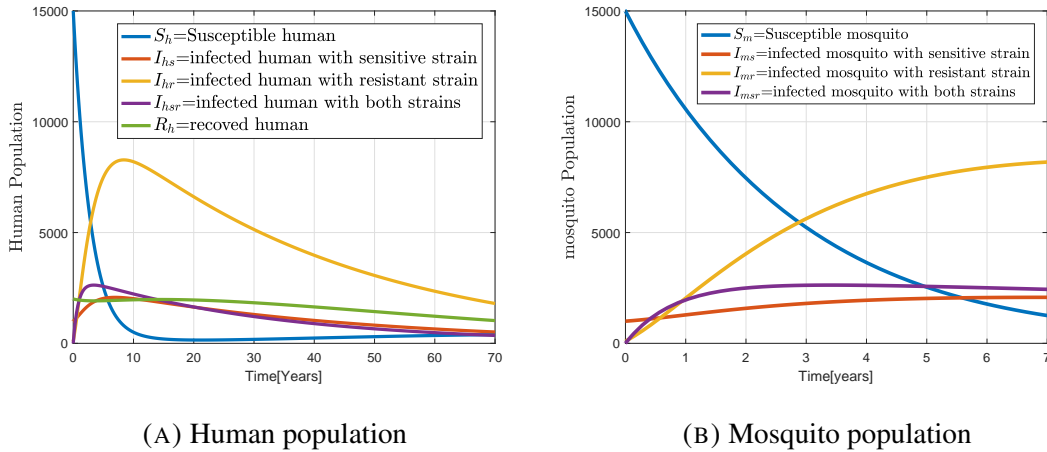


FIGURE 1. Dynamics of human population and mosquitoes population

Figures 1a and 1b show dynamics of malaria in human beings and in mosquitoes' populations. As malaria infection increases, susceptible human and mosquitoes decline while infected classes increase.

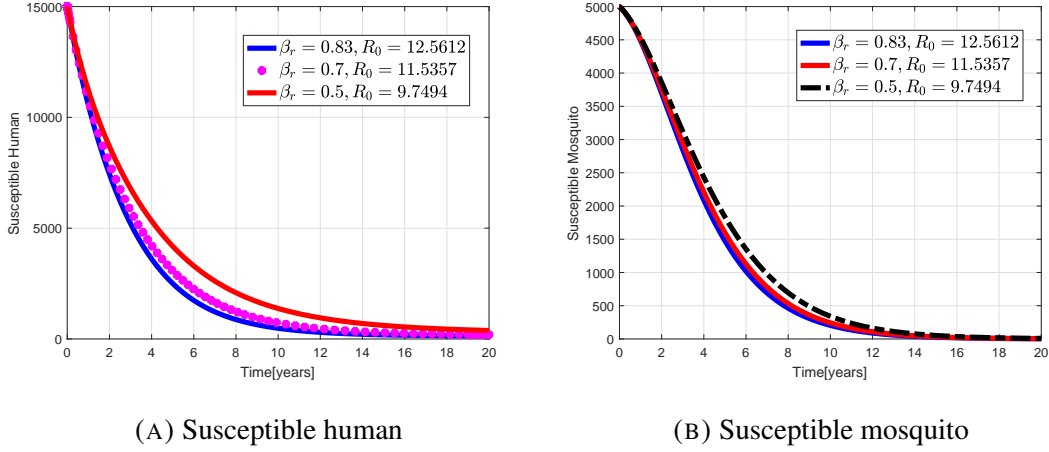


FIGURE 2. Variation of human transmission in susceptible classes

Susceptible humans and mosquitoes decrease as the rate of infection of malaria resistant strain in human β_r varies from 0.5 to 0.83 as demonstrated in Figures 2a and 2b.

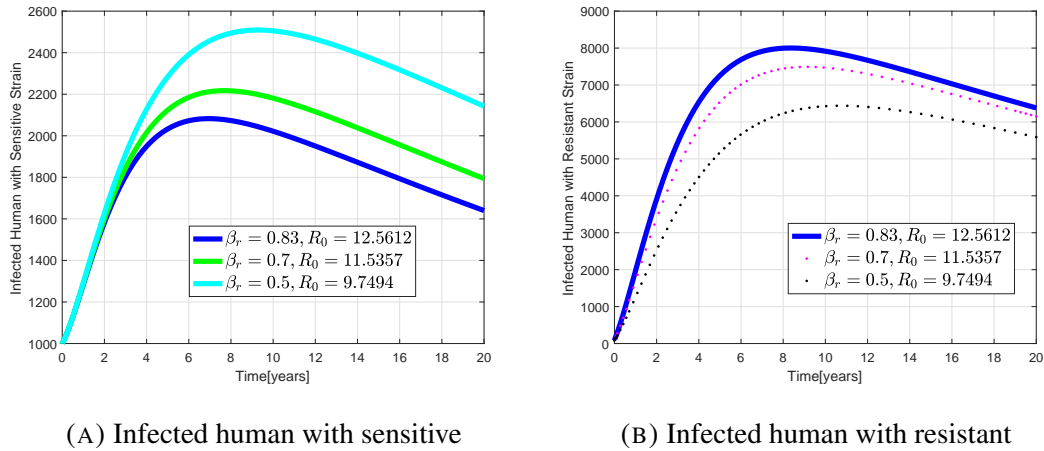
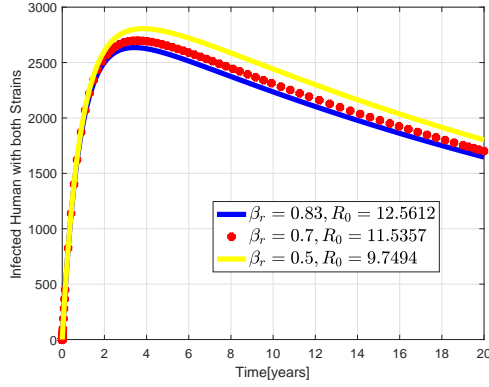
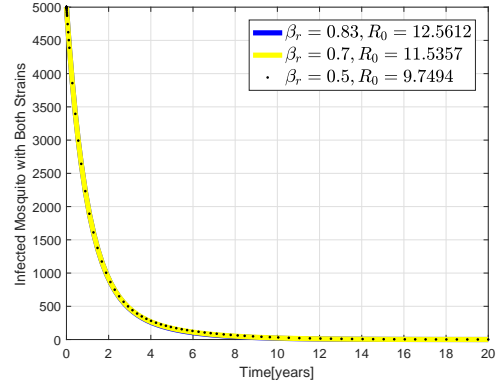


FIGURE 3. Variation of human transmission in infected human with sensitive and infected human with resistant

Human with sensitive strain decrease while infectious human with resistant strain increases due to high rate of malaria infection as demonstrated in Figures 3a and 3b.



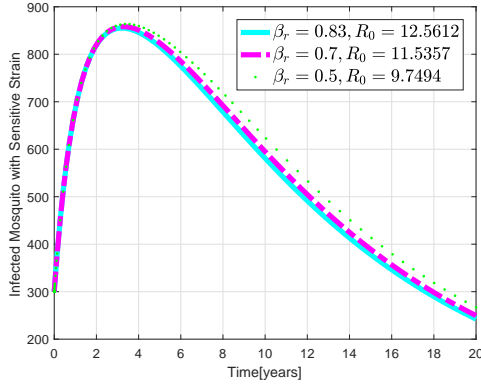
(A) Infected human with both strains



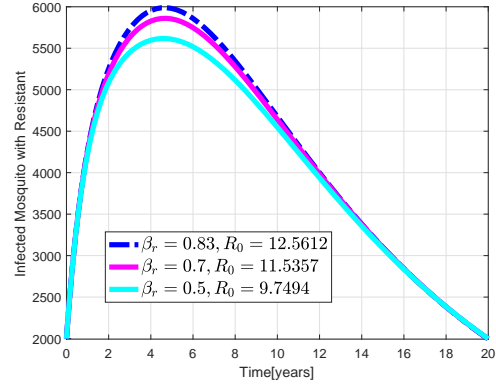
(B) Infected mosquito with both strains

FIGURE 4. Variation of human transmission in infected human and mosquitoes with both strain

It is further found that as human transmission rate increases, infectious human with both strains decrease and infectious mosquitoes with both strain decreases because of competition where resistant strain becomes fit. Therefore mosquitoes which are infected with both strain become infected with resistant strain as it is demonstrated in Figures 4a and 4b.



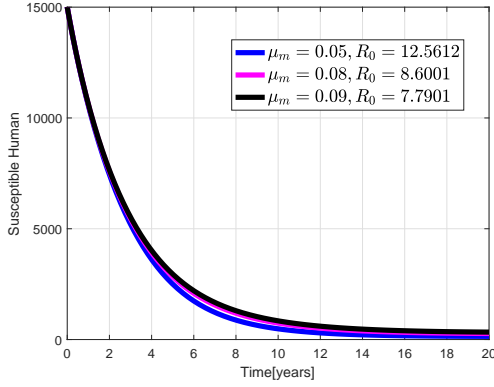
(A) Infected mosquito with sensitive strain



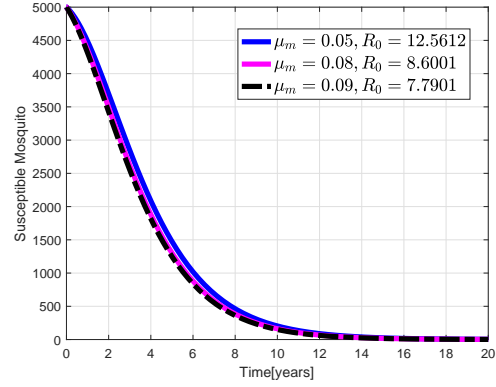
(B) Infected mosquito with resistant strain

FIGURE 5. Variation of human transmission rate in mosquitoes infected classes

Figures 5a and 5b show that as human transmission rate of malaria resistant strain varies from $\beta_r = 0.5$ to 0.83 , infectious mosquito with sensitive strain decreases while infectious mosquito with resistant strain increases in three years and reach maximum at five years and start declining from seventeen to twenty years.



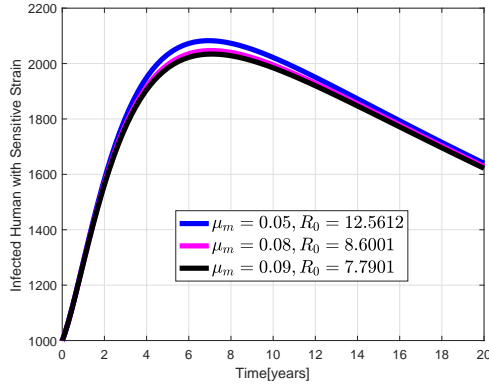
(A) Susceptible human



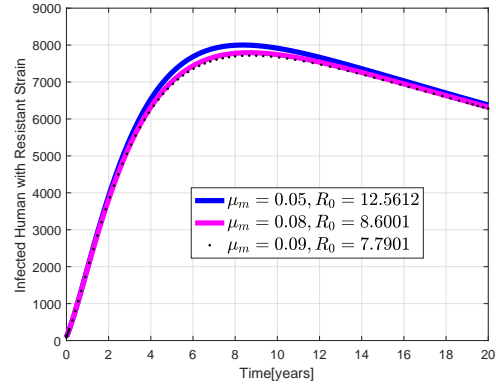
(B) Susceptible mosquito

FIGURE 6. Variation of natural death rate of mosquitoes in susceptible human and mosquitoes.

Figures 6a and 6b show that as natural death rate of mosquito increases from $\mu_m = 0.05$ to 0.09, susceptible human increase while susceptible mosquitoes decreases.



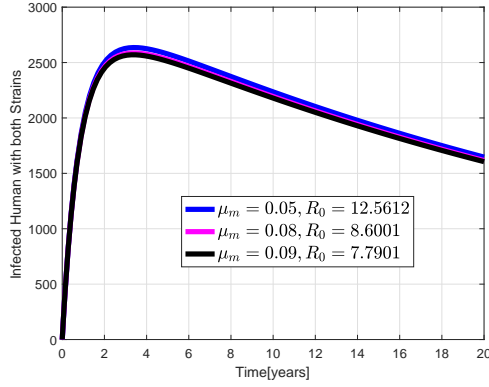
(A) Infected human with sensitive



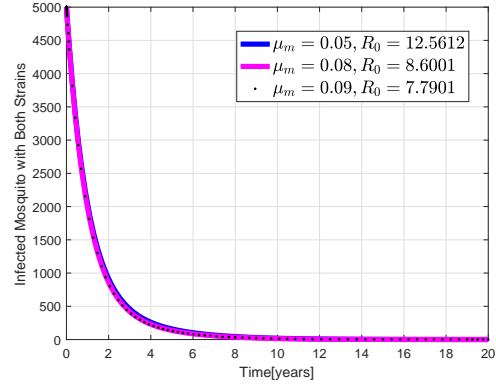
(B) Infected human with resistant

FIGURE 7. Variation of natural death rate of human in infected classes

It is found that as natural death rate of mosquito varies from $\mu_m = 0.05$ to 0.09, both infectious human with sensitive and with resistant strain decrease, as demonstrated in Figures 7a and 7b.



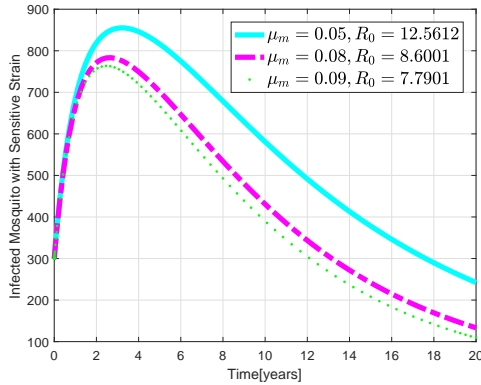
(A) Infected human with both strain



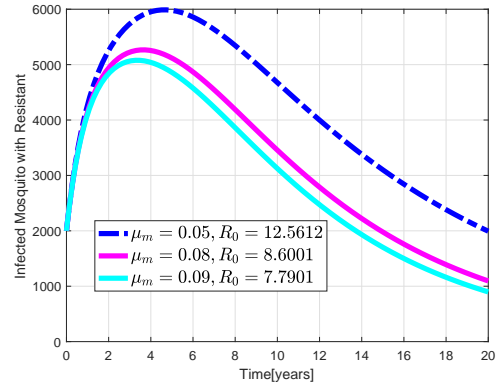
(B) Infected mosquito with both strain

FIGURE 8. Variation of natural death rate of mosquitoes in infected human and mosquitoes in both strains.

However as natural death rate of mosquito varies from $\mu_m = 0.05$ to 0.09 , both infectious human and mosquitoes with both strains decreases, as demonstrated in Figures 8a and 8b.



(A) Infected mosquito with sensitive



(B) Infected mosquito with resistant

FIGURE 9. Variation of natural death rate of mosquitoes in infected classes

Figures 9a and 9b show that as natural death rate of mosquito increases from $\mu_m = 0.05$ to 0.09 , infectious mosquitoes with sensitive and with resistant strain decreases.

5. Conclusion, Discussion and Recommendation

We developed and analyzed a mathematical model to explain the transmission dynamics of malaria sensitive and resistant strains with super infection. The basic reproduction number R_0 is computed and sensitivity index of each parameter with respect to the basic reproduction number R_0 is derived. The basic reproduction is given as a maximum of partial reproduction numbers due to sensitive strain R_{01} , resistant strain R_{02} and partial reproduction number R_{03} due to both strains: sensitive and resistant. Analysis shows that the rate of transmission of malaria with resistant strain β_r to human beings and mosquitoes' natural death rate μ_m are the most sensitive parameters to malaria transmission dynamics. Malaria infection increases in proportion to the rate at which malaria is transmitted to human beings and it decreases as mosquitoes' natural death rate increases. Mosquitoes' biting rate plays an important role in malaria transmission, these results are supported by numerical simulations. The study recommends that, strategies which are intended to increase mosquitoes' mortality will bring malaria infection under control.

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Conflict of Interests

The authors declare that there is no conflict of interests.

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